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Analgesic Abuse:

Maximal Tolerated Daily Doses of Acetylsalicylic Acid

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MOST analgesic drugs available over-the-counter (OTC) without a prescription contain one or more of the following: acetylsalicylic acid, phenacetin, paracetamol and caffeine. Paracetamol, B.P., is a metabolite of phenacetin and is frequently substituted for it. Compared with other analgesics, these drugs are considered to be relatively non-toxic and, therefore, are made available to the general public on the theory that every person has an inherent right, within certain limitations, to diagnose and treat his own ills. Control of these drugs by the Food and Drug Directorate of the Department of National Health and Welfare is confined to regulations mainly concerning purity and label instructions. Purity is checked by analysis of marketed products, and instructions on the label must meet governmental standards. The label must state the recommended daily dose. It is of considerable interest that studies in this department,[1-13] as summarized in Table I, indicate that if this government-approved daily dose is not exceeded, toxicity is not liable to occur.

On the other hand, there are no laws which prevent a person from taking more than the dose recommended on the label, provided there is no attempt to commit suicide. Our studies suggest that the recommended daily dose can be doubled, trebled or even quadrupled for a few days without producing serious toxic effects, but that continued use of high doses will invariably lead to intoxication and death. Recent surveys have shown that addicted persons take from 25 to more than 100 analgesic tablets per day[6] and from 0.5 to 1.5 kg. per year.[14] The amount of phenacetin,[6] paracetamol,[10] caffeine[12] and acetylsalicylic acid contained in such doses of analgesic tablets approaches that which produces death in albino rats given the drug once daily for 100 days. Headache is the most common reason for taking such large doses of analgesics; the addicted persons are usually over 40 years of age and are mostly women.[6, 14] In this connection, it is of interest that we have found all of these drugs, except caffeine, to be more toxic in female than in male rats. To exemplify this difference, values for the LD_{50} of phenacetin in male and female rats are cited in Table I; Coldwell and Boyd[3] reported similar findings for acetylsalicylic acid. Persons who take huge doses of analgesics usually have an extreme fear of pain.[6] If they are hospitalized it is usually for suspected renal papillary necrosis, and on leaving hospital they frequently revert to their analgesic abuse.[6] From the figures of Koch *et al.*[14] the incidence of analgesic abuse to doses producing severe toxicity may be calculated to be about the same as the incidence of narcotic addiction in Canada, namely, about 1 in 10,000.

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TABLE I.—A SUMMARY OF PUBLISHED STUDIES ON THE ORAL AND RECTAL TOXICITY OF ACETYLSALICYLIC ACID, PHENACETIN, PARACETAMOL AND CAFFEINE

Drug	*Route*	*Single or multiple doses*	*Species*	*$LD_{50} \pm SE$ (g./kg.)*	*Main clinical signs*	*Main autopsy signs*	*Reference number*
Acetylsalicylic acid	Oral	Single	Cat	>1	Vomiting		1
" "	Oral	Single	Dog	>1.0	Vomiting		1
" "	Oral	Single	Rat	0.92 ± 0.05	Anorexia, diarrhea, psychotic-like reactions, epistaxis and death following convulsions or cardiovascular collapse	Gastroenteritis, hepatitis, nephritis and pulmonary congestion	1
" "	Oral	Single	Guinea pig	1.19 ± 0.07	Similar to rat	Similar to rat	2
" "	Rectal	Single	Rat	0.79 ± 0.03	Similar to oral administration	Similar to oral administration	3,4
Phenacetin	Oral	Single	Cat	>2.0	Vomiting		5
"	Oral	Single	Dog	>2.0	Vomiting		5
"	Oral	Single	Female Rat	1.65 ± 0.35	Lethargy, ataxia, anorexia, oliguria and death in hypothermic coma	Gastroenteritis, hepatitis, nephritis, pulmonary edema and congestion, hydration and loss of organ weight	5
"	Oral	Single	Male rat	4.14 ± 0.71	Same as female	Same as female	
"	Oral	Single	Guinea pig	1.87 ± 0.07	Similar to rat	Similar to rat	2
"	Rectal	Single	Rat	Same as oral	Similar to oral administration	Similar to oral administration	7
"	Oral	Multiple	Rat	See Table VI	Inhibition of growth, diuresis, ataxia, pallor	Infection, stress reaction, organ atrophy and hydration, inhibition of spermatogenesis, renal papillary necrosis	6
Paracetamol	Oral	Single	Rat	3.71 ± 0.83	Similar to phenacetin	Liver necrosis and similar to phenacetin	8,9
"	Oral	Multiple	Rat	See Table VI	Inhibition of growth, diuresis, listlessness	Infection, stress reaction, organ congestion, testicular atrophy, hepatitis, nephritis	10
Caffeine	Oral	Single	Rat	0.19 ± 0.02	Anorexia, oliguria, ataxia, psychotic reactions, diarrhea and death following convulsions or cardiovascular collapse	Gastroenteritis, hepatitis, nephritis, and congestion and dehydration of organs	11
"	Oral	Single	Dog	>0.2	Vomiting		11
"	Oral	Single	Guinea pig	0.23 ± 0.02	Similar to rat	Similar to rat	2
"	Rectal	Single	Rat	Same as oral	Similar to oral administration	Similar to oral administration	7
"	Oral	Multiple	Rat	See Table VI	Psychoses, diuresis, infection at LD_{50} (100 days)	Encephalitis, gastric ulcers, nephritis, hepatitis, inhibition of gonads at LD_{50} (100 days)	12,13

The problem of analgesic abuse has been studied experimentally in this laboratory since reports on the "phenacetin kidney" appeared some 10 years ago. As these studies were concerned with the production of severe toxicity and death, they were performed upon laboratory animals. Table I lists significant data taken from representative publications, in each of which will be found a summary of the relevant literature. The table contains information on the clinicopathologic syndrome of intoxication to oral administration of single doses at the range of the LD_{50} and of daily doses given to rats for 100 days, or for one-tenth their normal lifespan, at the range of the LD_{50} (100 days). (The latter expression refers to the daily dose which kills 50% of the animals during administration for 100 days.) Because of reports of toxicity from analgesic suppositories (mostly for children) studies were made on rectal administration, and representative publications are cited in Table I.

These studies have shown that the syndromes of intoxication from single and multiple doses of these drugs have many features in common.

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When given as mixtures, the toxicity of the mixture is a sum of the toxicity of the ingredients.[2, 15] Doses per kg. producing severe toxicity in animals are within the range of possible human consumption. In particular, these studies indicate that nephrotoxicity is but part of the reaction to chronic dosing. This was found to apply to acetylsalicylic acid in the project herein reported, which is the last of our studies on analgesic toxicity at the range of the oral LD_{50} (100 days) in albino rats.

METHODS

The general purpose of this project was to determine the maximal oral LD_0 (100 days) (not causing the death of any of the experimental animals during daily oral administration for 100 days); LD_{50} (100 days) (producing death in 50% of the animals); and minimal LD_{100} (100 days) (minimal daily dose killing all animals). The details and rationale of the method have been recently reviewed.[16]

These experiments were performed upon 252 young male albino rats.* Their initial mean ± S.D. body weight was 158 ± 8 g. They were fed Purina laboratory chow checkers.†

Acetylsalicylic acid, B.P., U.S.P., was administered each morning for five days a week in a series of fractions of the LD_{50} which was found to be 1.48 ± 0.04 g. per kg. in young male rats.[3] When acetylsalicylic acid was given for longer than one week, the total weekly dose was divided by 7 to obtain the average daily dose. Each daily dose was given for 100 days or until 60% of the animals had died, whichever occurred first. The daily doses selected were 0.21, 0.29, 0.36, 0.43, 0.50, 0.57, 1.00, 1.25 and 1.50 g. per kg.; each dose was given to 20 animals and 8 controls received distilled water. Each dose was suspended in distilled water using 0.25% gum tragacanth and was given intragastrically by means of a cannula attached to a syringe in a volume of 20 ml. per kg. body weight. Pair-fed controls were not introduced since pilot experiments indicated that food intake was not reduced, except premortally, at the LD_{50} (100 days).

Clinical measurements were made upon each rat housed singly in a metabolism cage for cageside observations on the day before the beginning of drug administration and at weekly (or shorter if indicated) intervals thereafter. The measurements made were body weight gain per week in grams, food intake in g. chow per kg. body weight per 24 hours, water intake in ml. per kg. per 24 hours, colonic temperature, urinary volume in ml. per kg. per 24 hours, urinary output of glucose and protein in mg. per kg. per 24 hours, urinary pH on 24-hour samples and other signs semi-quantitated in clinical units of 1+ to 4+.

*Canadian Breeding Laboratories, St. Constant, Quebec.
†The Ralston Purina Company, Woodstock, Ontario.

TABLE II.—PATHOLOGICAL LESIONS SEEN ON GROSS EXAMINATION OF BODY ORGANS IN RATS WHICH DIED FROM DAILY ORAL ADMINISTRATION OF ACETYLSALICYLIC ACID

Observation	*Dosage range*	*% incidence in 142 autopsies*
Loss of skin fat	All doses	100
Wasting of muscle	All doses	100
Atrophy of the thymus gland	All doses	100
Gastric hypertrophy	All doses	78
Pneumonitis	All doses	64
Dark liver	All doses	37
Dark spleen	All doses	36
Pallor of body organs	Large doses	25
Inflamed small bowel	All doses	20
Pale liver	Small doses	18
Gastric ulcers	Large doses	14
Gastric inflammation	Large and medium doses	13
Pale or soft kidney	Low and medium doses	11
Congested brain	Medium doses	8
Blood in the colon	Large doses	4
Congested thymus gland	Medium doses	4
Pale spleen	Medium doses	3
Congested testes	Small doses	2

Gross and microscopic pathology were recorded on animals which died and which could be autopsied within one hour of death to avoid the postmortem changes recorded by Boyd and Knight[17] (Table II). Microscopic examination was made on sections from the tissues listed in Table III which were fixed in Lillie's buffered formalin and stained with hematoxylin-phloxine-saffron.

The fresh weight in grams of organs listed in Table IV was recorded in survivors at 100 days or after 60% of animals had died, whichever occurred first. The contents of the gastrointestinal organs were removed by water-washing and milking before tissue fresh weight was measured. The sample of skeletal muscle was the left half of the muscle layer of the ventral abdominal wall. Organs were weighed to 0.1 mg. on a Mettler* semimicrogramatic balance, with the exception of skin and residual carcass which were weighed to 0.01 g. The water content of the same organs was determined by drying aliquots to constant weight in a Fisher forced-draft isotemp oven at 95° C. The sample of skin for water analysis was taken from the dorsolumbar region after clipping the hair. Residual carcass was cut into small pieces, homogenized in a Waring blender, and a sample weighed for water analysis. Water levels were calculated as g. per 100 g. dry weight of tissue.

*Fisher Scientific Company, Don Mills, Ontario.

TABLE III.—HISTOPATHOLOGIC OBSERVATIONS ON THE ORGANS OF ALBINO RATS WHICH DIED FOLLOWING DAILY ADMINISTRATION OF LARGE DOSES OF ACETYLSALICYLIC ACID

Organ	*Histopathology*
Adrenal glands	Lipoid droplets prominent in the cortical zones at all doses
Brain	Normal at LD_{50} (100 days) and less; meningeal congestion and granulocyte infiltration with occasionally cerebral capillary hemorrhages at higher doses
Gastrointestinal tract:	
Cardiac stomach	Hypertrophy of the stratified squamous epithelium, muscularis mucosa and muscularis externa at all doses; occasionally capillary-venous congestion of the lamina propria and granulocyte-infiltrated ulcers at doses above LD_{50} (100 days)
Pyloric stomach	Hyperemia and congestion with occasionally necrotic or partially fibrosed ulcers at doses above the LD_{50} (100 days)
Small bowel	Normal appearance; occasionally hyperemic
Cecum	Normal appearance
Colon	Normal appearance
Heart	Normal at LD_{50} (100 days) and less; capillary congestion and hemorrhage occasionally from larger doses
Kidneys	Capillary congestion of the loop region from all doses; fatty degeneration and necrosis of the tubules from doses above the LD_{50} (100 days)
Liver	Sinusoidal congestion; pale-staining and mild fatty degeneration and necrosis of hepatic cells from all doses
Lungs	Congestion and edema at all doses
Muscle (ventral abdominal wall)	Normal appearance
Salivary (submaxillary) gland	Occasionally deficiency of zymogenic granules in the serous glands.
Skin	Occasionally ischemic
Spleen	Occasionally congested; occasionally excess macrophages
Testes	Normal at LD_{50} (100 days) and less; interstitial congestion and mild inhibition of spermatogenesis at larger doses
Thymus gland	Loss of thymocytes, more marked with increasing doses

Sufficient animals given the two lowest doses of acetylsalicylic acid were alive at 100 days to permit a pilot study of the effect of abrupt withdrawal of the drug. This was done on 15 drug-treated rats and on 4 controls. Locomotor activity was measured in a Wahmann activity drum at weekly intervals during the last three weeks of drug (or distilled water) administration and every second day for 14 days following abrupt withdrawal. The clinical measurements noted above were also recorded every second day for two weeks following withdrawal of acetylsalicylic acid.

The results were analyzed statistically by application of t-tests to significance of differences between means and by regression analysis of such differences

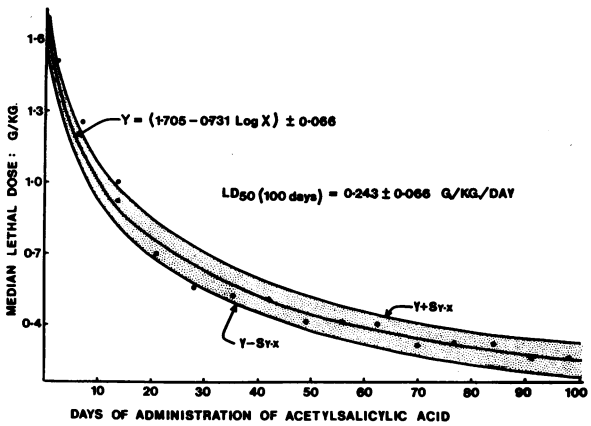

Fig. 1.—The regression, on days of oral administration of acetylsalicylic acid, of a daily dose which killed 50% of the animals at progressive intervals. The regression line was calculated by the method of least squares. The shaded area includes the estimated value of Y plus its standard error (Y + Sy.x) and minus its standard error (Y — Sy.x).

on time or daily dose of drug.[16] The LD_{50} was calculated by the linear regression method of Boyd.[18]

RESULTS

Values of the LD_{50} calculated at weekly intervals following the beginning of daily administration of acetylsalicylic acid are plotted against duration of drug administration in Fig. 1. The estimating equation of the regression line was calculated by the method of least squares and found to be $Y = (1.705 - 0.731 \log X) \pm 0.066$. The LD_{50} (100 days) or daily dose which killed 50% of animals during 100 consecutive days of oral administration was found to be 0.243 ± 0.0661 g. per kg. per day, this value being calculated by substituting 2 for log X in the estimating equation since the log of 100 (days) is 2.

The maximal LD_0 (100 days), or largest daily dose which failed to kill any animal of the group when given by intragastric tube for 100 consecutive days, was similarly calculated to be 0.098 ± 0.032 g. per kg. per day. The minimal LD_{100} (100 days), or smallest daily oral dose which killed all animals after 100 consecutive days, was found to be 0.409 ± 0.145 g. per kg. per day.

With certain exceptions to be noted later, each daily dose of drug produced an effect on each parameter which did not differ significantly from one weekly measurement to the next. The weekly differences from controls were calculated as $((\bar{X}_d - \bar{X}_c)/\bar{X}_c) \times 100$ where $\bar{X}_d$ was the mean of measurements in the drug-treated rats and $\bar{X}_c$ in their respective controls. The mean of the weekly changes from controls was calculated for each daily dose and these mean weekly

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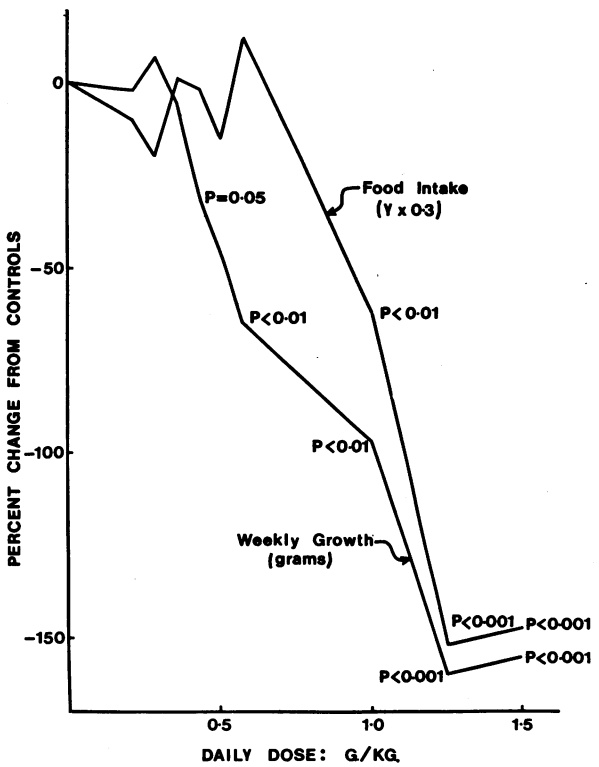

Fig. 2.—Growth rates and food intake in albino rats given daily doses of acetylsalicylic acid. The results are calculated as mean per cent changes from controls given water orally but no acetylsalicylic acid. The ordinate value for food intake is multiplied by 0.3 to obtain actual percentage changes. Mean percentage changes significantly different from zero at P = 0.05 or less are indicated by their P values.

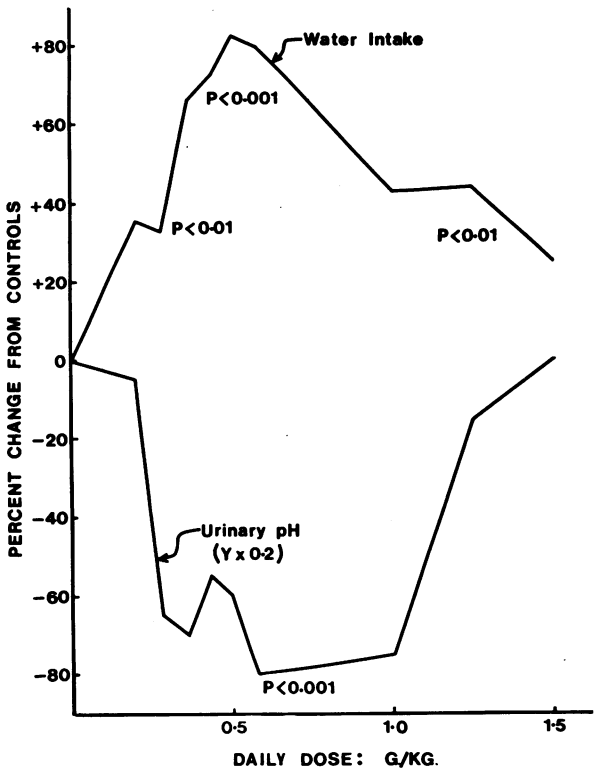

Fig. 3.—The polydipsia and aciduria of intoxication due to acetylsalicylic acid in relation to daily oral dose of the drug. The results for water intake and urinary pH are expressed as mean per cent change from controls. Note that the ordinate value for urinary pH must be multiplied by 0.2 to obtain mean per cent changes. Statistically significant changes are indicated by their P values.

per cent changes were then plotted against the daily dose of acetylsalicylic acid. Changes in growth rate and food intake are shown in Fig. 2. Growth and food intake were not depressed until the daily dose exceeded the LD_{50} (100 days). Colonic temperature was not significantly altered at any daily dose.

While food intake was unchanged at the LD_{50} (100 days), water intake was significantly increased (Fig. 3). The polydipsia reached a peak at doses of the order of the LD_{100} (100 days) and thereafter began to decline. The degree of polydipsia was related to the degree of aciduria.

The administration of increasing daily doses of acetylsalicylic acid was associated with increasing proteinuria, diuresis and drowsiness. Of these signs, only the diuresis was present to a statistically significant degree at doses in the range of the LD_{50} (100 days), but at this dose the degree of drowsiness was significant at P slightly less than 0.05.

Drowsiness at the LD_{50} (100 days) alternated with signs of stimulation of the nervous system. These included hyperreflexia, or increased response to stimuli such as prodding or blowing against the grain of the hair, piloerection, tachypnea, dyspnea (mainly deep breathing) and tachycardia. As the daily dose reached the range of the LD_{100} (100 days), these signs disappeared and the animals passed into a state of hypokinesia. Some epistaxis appeared at the LD_{50} (100 days) and disappeared as the daily dose exceeded 1 g. per kg. per day, possibly because most of the animals given these large doses died in the first week of administration.

Certain clinical signs appeared only in animals given daily doses of acetylsalicylic acid in excess of the LD_{100} (100 days). Death in these animals was preceded by marked prostration and glycosuria, and there was considerable blood in the stool.

Some clinical signs appeared only after daily administration of acetylsalicylic acid for a certain period of time. Soft stools, epistaxis, sialorrhea and dacryorrhea appeared after two to four weeks, reached a peak during the second month and thereafter disappeared. All of these signs appeared with doses in the range of the LD_{50} (100 days).

The immediate cause of death in animals given daily doses greater than the LD_{100} (100 days) was convulsions followed by respiratory

failure. The cause of death at the LD_{50} (100 days) was respiratory failure in deep hypothermic coma following a period of anorexia, oligodipsia, oliguria, marked proteinuria and increasing pallor.

A summary of the lesions noted by gross examination of body organs at autopsy is given in Table II. The most commonly observed changes were loss of skin fat, wasting of skeletal muscle, atrophy of the thymus gland, hypertrophy of the stomach (especially of the cardiac part) and pneumonitis.

Histopathologic observations are indicated in Table III. The most common signs at and below the LD_{50} (100 days) were capillary-venous congestion of the kidneys, liver and lungs, atrophic changes in the salivary and thymus glands and hypertrophy of cardiac stomach. Larger doses produced degenerative changes in the kidneys and liver, cerebral hemorrhage, gastric ulcers, inhibition of spermatogenesis, a stress reaction in the adrenal and thymus glands, pneumonitis, and meningeal and myocardial capillary congestion. A photomicrograph of the lesions in brain is shown in Fig. 4.

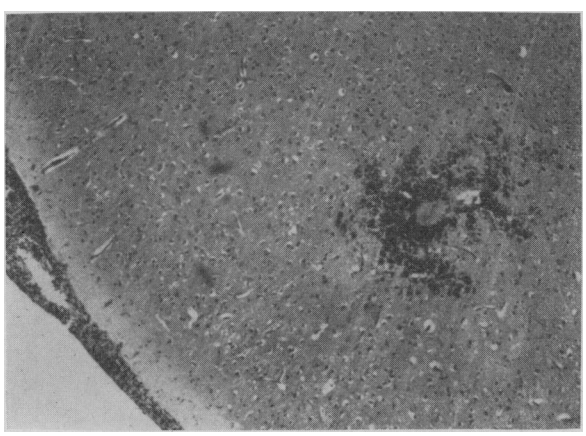

Fig. 4.—A photomicrograph of the brain of a rat which died after 43 days of administration of acetylsalicylic acid in a dose of 0.43 g. per kg. per day showing capillary-venous congestion and granulocyte infiltration of the meninges and an area of capillary hemorrhage (to right of centre) in the brain.

Shifts in the fresh weight of body organs are summarized in Table IV. At the LD_{50} (100 days) and in higher doses, acetylsalicylic acid produced loss of weight in muscle and skin and in large doses in almost all organs. The stomach and, to a lesser degree, the liver tended to weigh more than in the controls. There was a stress reaction in the adrenal and thymus glands which was more marked as the dose of acetylsalicylic acid was increased.

Alterations in the water content of body organs are indicated in Table V. It may be seen

TABLE IV.—CHANGES IN THE FRESH WEIGHT OF BODY ORGANS OF ALBINO RATS FOLLOWING DAILY ORAL ADMINISTRATION OF LARGE DOSES OF ACETYLSALICYLIC ACID*

Organ	*Doses in the range of the LD_{50} (100 days) (N = 16 plus 16 controls)*	*Doses in the range of the minimal LD_{100} (100 days) (N = 24 plus 24 controls)*	*Doses above the minimal LD_{100} (100 days) (N = 32 plus 32 controls)*
Adrenal glands	+ 2.5	+ 8.5**	+10.0**
Brain	− 1.6	− 3.7	− 0.8
Gastrointestinal tract:			
Cardiac stomach	+21.0†	+22.9†	+20.4†
Pyloric stomach	+20.1†	+13.0†	− 3.2
Small bowel	0.0	+ 4.0	− 3.6
Cecum	− 1.3	+15.4**	− 1.9
Colon	+ 8.1	+ 1.5	−10.3**
Heart	−10.0**	− 4.4	− 9.3**
Kidneys	+ 1.2	− 1.7	− 5.3
Liver	+16.2†	+ 7.0**	− 3.1
Lungs	− 7.1	+ 2.4	− 7.3**
Muscle (ventral abdominal wall)	− 23.2†	−27.7†	−25.0†
Salivary (submaxillary) glands	−12.1**	−17.5†	−17.1†
Skin	−19.8†	−29.3†	−24.1†
Spleen	+ 7.1	+ 1.9	− 4.7
Testes	− 3.1	− 0.3	− 2.5
Thymus gland	−32.6†	−41.0†	−55.0†
Residual carcass	−12.1†	−19.5†	−16.9†
Total body weight	− 8.5**	−15.4†	−14.6†

*Fresh weight was measured in grams. The results are expressed as mean per cent change from respective controls, specifically as $((\bar{X}_d - \bar{X}_c)/\bar{X}_c) \times 100$ where $\bar{X}_d$ is the mean in the drug-treated group and $\bar{X}_c$ in the corresponding controls given no acetylsalicylic acid. **indicates that $\bar{X}_d - \bar{X}_c$ was significant at P = 0.05 to 0.02 and † at P = 0.01 or less.

that part of the increase in weight of the gastrointestinal tissues was due to hydration. Loss of organ weight was not due to loss of organ water but to loss of dry weight, since most tissues were slightly hydrated.

Abrupt withdrawal of acetylsalicylic acid at 100 days disclosed a mild degree of physical dependence as evidenced by a mild hyperkinetic withdrawal syndrome. Indications of this were an increase in locomotor activity to

TABLE V.—CHANGES IN THE WATER CONTENT OF BODY ORGANS OF ALBINO RATS FOLLOWING DAILY ORAL ADMINISTRATION OF LARGE DOSES OF ACETYLSALICYLIC ACID*

Organ	*Doses in the range of the LD_{50} (100 days) (N = 16 plus 16 controls)*	*Doses in the range of the minimal LD_{100} (100 days) (N = 24 plus 24 controls)*	*Doses above the minimal LD_{100} (100 days) (N = 32 plus 32 controls)*
Adrenal glands	+1.4	−3.6	+ 1.7
Brain	+1.0	−1.3	+ 0.5
Gastrointestinal tract:			
Cardiac stomach	−1.5	−2.7	+ 2.6
Pyloric stomach	−2.8	+5.9**	+ 8.5†
Small bowel	−0.7	+9.9**	+ 2.0
Cecum	+1.5	+8.5**	+ 9.7†
Colon	+0.8	+9.3**	+ 5.0**
Heart	−1.4	+3.5	+ 4.6
Kidneys	+3.1	+0.9	+ 8.4†
Liver	+2.9	+2.5	+ 0.2
Lungs	+1.7	−0.5	+ 1.3
Muscle (ventral abdominal wall)	+2.2	+4.2	+ 2.8
Salivary (submaxillary) glands	+1.4	+3.5	+ 1.6
Skin	−2.1	+5.1**	+11.8†
Spleen	−0.6	+3.9	+ 6.5**
Testes	−2.2	+2.0	+ 3.0
Thymus gland	−1.4	+2.6	+ 4.4
Residual carcass	−4.2	+1.7	+ 3.2

*Water content was measured as grams water per 100 g. dry weight of tissue. The results are expressed as mean per cent change from controls, specifically as $((\bar{X}_d - \bar{X}_c)/\bar{X}_c) \times 100$ where $\bar{X}_d$ is the mean in the drug-treated animals and $\bar{X}_c$ in the corresponding controls.** indicates that $\bar{X}_d - \bar{X}_c$ was significant at P = 0.05 to 0.02 and † at P = 0.01 or less.

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double that of the controls, hyperreflexia and piloerection for the first 7 to 10 days. Food and water intake were above values in the controls and the growth rate increased; the diuresis, proteinuria and other clinical signs gradually disappeared and there were no deaths.

DISCUSSION

The LD_{50} (100 days) of acetylsalicylic acid given intragastrically was found to be 0.243 ± 0.066 g. per kg. per day, which is 16.4 ± 0.5% of the oral LD_{50} (1 dose) or single dose given orally on an empty stomach which killed 50% of young male albino rats as found by Coldwell and Boyd.[3] This percentage has been termed the C/A (Chronic/Acute) LD_{50} (100 days) Index and it is a useful index of chronic toxicity. The lower the value of the C/A LD_{50} (100 days) Index, the lower the fraction of an acute LD_{50} (1 dose) which can be tolerated on daily administration and hence the relatively more toxic the drug for chronic use.

TABLE VI.—THE LD_{50} (100 DAYS) OF SEVERAL DRUGS EXPRESSED AS A PERCENTAGE OF THE LD_{50} (1 DOSE) TO YIELD THE C/A LD_{50} (100 DAYS) INDEX*

Drug	*LD_{50} (100 days) ± S.E.***	*LD_{50} (1 dose) ± S.E.***	*C/A LD_{50} (100 days) Index*
Atropine sulfate	0.078 ± 0.005[19]	0.588 ± 0.085[20]	13.2 ± 0.8
Acetylsalicylic acid	0.243 ± 0.066	1.48 ± 0.004[3]	16.4 ± 0.5
Pilocarpine nitrate	0.156 ± 0.020[21]	0.911 ± 0.111[22]	17.1 ± 2.2
Paracetamol	0.77 ± 0.02[10]	3.71 ± 0.83[3]	20.6 ± 0.5
Phenacetin	1.12 ± 0.02[6]	4.14 ± 0.71[6]	27.1 ± 0.5
Benzylpenicillin	4.14 ± 0.20[23]	6.7 ± 0.1[24]	61.8 ± 3.0
Sodium chloride	2.69 ± 0.12[25]	3.75 ± 0.43[26]	71.7 ± 3.2
Caffeine	0.150 ± 0.003[12]	0.192 ± 0.018[11]	78.2 ± 1.6
Sucrose	34.4 ± 0.55[27]	35.4 ± 7.0[28]	97.2 ± 1.6

*Figures in superscript are the number of the reference containing the data quoted.

**The results are expressed as g. per kg. body weight. The drugs were given intragastrically to albino rats in all instances except that atropine sulfate was given intramuscularly to rabbits.

Several values of the C/A LD_{50} (100 days) Index have been assembled in Table VI. It may be seen that drugs which are a part of the normal diet, such as table salt, caffeine and table sugar, have a high index indicating relative safety for chronic daily use. Acetylsalicylic acid, paracetamol and phenacetin rank with drugs such as atropine and pilocarpine and have a relatively low index of chronic toxicity, indicating that chronic use of relatively low fractions of the LD_{50} (1 dose) can produce toxicity. Hayes[29] has also proposed relating a 90-day LD_{50} to the LD_{50} (1 dose).

Daily doses of acetylsalicylic acid of the order of 0.1 to 0.2 g. per kg. produced intoxication and death. This dose, on a body-weight basis, corresponds to a person weighing 60 kg. or 130 lbs. taking at one time 18 to 36 tablets per day of acetylsalicylic acid, 0.3 g. or 5 grains per tablet. If distributed throughout the day, toxicity would probably be less marked. We have found in current studies that large doses of phenacetin are less toxic if taken by rats in their diet over the 24 hours than if given once daily by intragastric cannula. If these results on phenacetin apply to acetylsalicylic acid and can be extrapolated to man, they suggest that daily doses of some 25 to 100 tablets of acetylsalicylic acid could eventually produce death after long-term use. The number of tablets required to produce a fatal outcome would be lower in children and could be lower in persons exposed to other noxious influences.

The basic cause of death from an LD_{50} (100 days) of acetylsalicylic acid and of the other drugs listed in Table VI appears to be inability of the body to detoxify rapidly such large doses of a chemical agent. Body organs primarily affected are those which receive a large percentage of the blood pumped from the heart. The lungs become congested and susceptible to infection. The meninges and brain become hyperemic and mental reactions are common. The heart of the young rat is fairly resistant to toxic doses of drugs, but the capillaries of the myocardium are often dilated. The liver is the principal organ of detoxification and it is susceptible to degenerative changes. The kidney is the main organ of elimination, and as toxic amounts of the drug concentrate along the nephron at progressive stages, damage becomes progressively greater. Renal papillary necrosis was found in the studies on phenacetin[6] but not on acetylsalicylic acid, caffeine[12] or paracetamol.[10]

The gastrointestinal tract bears the brunt of toxic doses of chemicals taken by mouth, and it might be expected that irritant inflammatory reactions would be common. This is true of single doses given at the range of the LD_{50} (1 dose) as shown in Table I. At the LD_{50} (100 days), however, the gastrointestinal mucosa appears to have a marked ability to withstand the irritant effect of toxic doses and hypertrophy is fairly common, as seen with acetylsalicylic acid (Tables III and IV) and particularly with starch.[30] Hypertrophy of the stomach may be due to distension produced by repeated daily administration of large volumes of water which are regularly given as the vehicle for administration of drugs.[30]

Gastric ulcers occur when acetylsalicylic acid and many other drugs are given at the LD_{50} (100 days) and higher doses. They may be due to the direct irritant action of acetylsalicylic acid or be secondary to a stress reaction. Constantopoulos, Kovacs and Melville[31] reported that ace-

tylsalicylic acid in oral doses of 0.12 g. per kg. per day for 21 days augmented the histamine content of guinea-pig intestine, and Croft[32] considers that large doses of acetylsalicylic acid may cause a loss of protective mucosal cells at a rate faster than they are replaced. The appearance of blood in the stools may be related to epistaxis, and both may be related to inhibition of prothrombin production in the liver as discussed by Dacie.[33]

Other tissues were affected by acetylsalicylic acid in doses at the range of the LD_{50} (100 days). There was some atrophy of the thymus gland, the salivary glands, skeletal muscle, skin and testes. Testicular atrophy was not as marked as that recorded at the LD_{50} (100 days) of phenacetin[6] and paracetamol[10] but has been previously noted in mice.[34]

Abrupt withdrawal of acetylsalicylic acid after administration for 100 days disclosed a very mild abstinence syndrome which suggested a very mild degree of physical dependence. Similar results were obtained with phenacetin,[6] paracetamol[10] and caffeine.[12] While the abstinence syndrome was mild, it was nevertheless present, and this suggests that some persons could develop a degree of physical dependence on these analgesic agents.

CONCLUSIONS

The maximal oral LD_0 (100 days) of acetylsalicylic acid, or largest dose producing no deaths when given by mouth daily for 100 days to albino rats, was found to be 0.098 ± 0.032 g. per kg. per day and the LD_{50} (100 days) 0.243 ± 0.066 g. per kg. per day. At these doses, acetylsalicylic acid produced no anorexia and no loss of body weight. It did produce polydipsia, aciduria, diuresis, drowsiness, hyperreflexia, piloerection, rapid and deep respiration, tachycardia and, during the second month, soft stools, epistaxis, sialorrhea, dacryorrhea and death in hypothermic coma. Autopsy disclosed the presence of a hypertrophied stomach, renal congestion, mild hepatitis and pneumonitis. In survivors there were found atrophy of the thymus and salivary glands, loss of weight in skeletal muscle and skin, an increase in liver weight and variable or insignificant shifts in organ water content.

Larger daily doses of acetylsalicylic acid produced an increasing anorexia, loss of body weight, polydipsia, aciduria, diuresis, proteinuria, glycosuria, drowsiness, prostration and hemofeces. At autopsy were found a stress reaction in the adrenal and thymus glands, meningeal congestion, cerebral capillary hemorrhage, gastric ulcers, myocardial congestion, degenerative changes in the kidneys and liver, pneumonitis, inhibition of spermatogenesis, an increase in weight and water content of the liver and gastrointestinal tissues, atrophy of muscle and skin, and atrophy and hydration of most other body organs.

Abrupt withdrawal at 100 days was accompanied by a mild hyperkinesia lasting for 7 to 10 days.

Summary Acetylsalicylic acid given orally to albino rats in doses of 0.24 ± 0.07 g. per kg. body weight per day killed 50% of the animals over a period of 100 days (one-tenth of their normal lifespan). The syndrome of toxicity included meningoencephalitis, pneumonitis, myocarditis, hepatitis and nephritis similar to the syndrome found in corresponding studies on phenacetin, paracetamol and caffeine. From calculations it is suggested that the continuous daily ingestion of 25 to 100 5-grain tablets of acetylsalicylic acid could eventually produce a similar intoxication in man. In Canada the incidence of addiction to such doses of freely available analgesics appears to be of about the same order as the incidence of addiction to narcotics.

Résumé Quelle est la dose maximum d'acide acétylsalicylique que peut tolérer l'être humain après ingestion quotidienne continue de cette drogue? Pour l'établir, on a commencé par le donner *per os* à des rats albinos, à la dose quotidienne de 0.24 ± 0.07 g par kg de poids corporel. Cette dose a causé la mort de 50% des animaux en l'espace de 100 jours (période représentant le dixième de leur longévité normale). Les symptômes toxiques comprenaient: méningo-encéphalite, pneumonite, myocardite, hépatite et néphrite, semblables au syndrome toxique constaté au cours d'études correspondantes sur la phénacétine, le paracétamol et la caféine. En interpolant, on arrive à la conclusion que l'ingestion quotidienne continue de 25 à 100 comprimés d'acide acétylsalicylique à 5 grains chacun pourrait produire une intoxication similaire chez l'homme. Au Canada, la fréquence de la toxicomanie, à des doses aussi éléves d'analgésiques que l'on peut se procurer librement, est à peu près du même ordre que la fréquence de la narcomanie.

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A Sign of Schizophrenia:

Clinical Response of Possible Significance Observed During Electroconvulsive Therapy

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THIS paper describes discrete variations in seizure patterns of psychiatric patients undergoing convulsive therapy and, in particular, a specific type of hand response observed under these circumstances in some patients. Clinically, this particular hand response was noticed most frequently in patients suffering from schizophrenia and, to a lesser extent, in women with affective disorders.

Electroconvulsive therapy (ECT), introduced by Cerletti and Bini[5] in 1938, is in general use for the treatment of schizophrenia and affective disorders. The main reason for observation of the patient during ECT is to ensure that a grand mal seizure occurs and that recovery is satisfactory. The seizure, proceeding through the tonic and clonic phases to subsequent relaxation, is described in standard textbooks of psychiatry,[14] but to date no significance appears to have been attributed to variations in the pattern of the convulsion.

The first intimation to one of us (P.R.) that the details of the seizure pattern might be of some clinical significance was in 1958, when a catatonic schizophrenic undergoing ECT showed a classical *schnauzkrampf* sign during the convulsion. This sign, first described by Kahlbaum[13] as a "snout-like protrusion of the lips", is usually considered diagnostic of catatonic schizophrenia when observed under normal clinical conditions. It had not been noted previously in this patient and its occurrence during ECT seemed to confirm the clinical diagnosis.

In 1962 attention was again drawn to the pattern of the ECT seizures when, during the clonic phase of the convulsion, the hands of a schizophenic patient were seen to make rapid "writing" movements with the pointing index fingers in space. These movements were so marked that the lines in the Rubaiyat of Omar Khayyam[7] were recalled:

> "The Moving Finger writes; and having writ,
> Moves on."

This association stimulated a more careful watch for the "writing" finger response, and it was next observed in another schizophrenic, who simultaneously showed a *schnauzkrampf* sign during the ECT. Conjecture was thus further stimulated: "What was the 'message' of the writing fingers?" Thereafter all patients undergoing convulsive therapy were observed in an attempt to answer this question.

DESCRIPTION OF RESPONSE

The hand response that was first noticed and that seemed to simulate writing movements consisted of complete extension of the index finger

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